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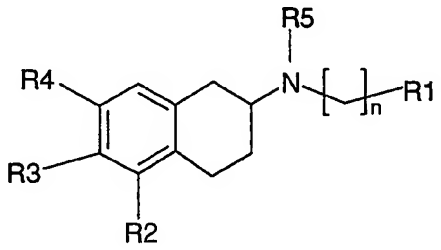
(54) UTILISATION DE 2-AMINOTETRALINES SUBSTITUEES POUR LE TRAITEMENT PROPHYLACTIQUE DE LA MALADIE DE PARKINSON

(54) USE OF SUBSTITUTED 2-AMINOTETRALINES FOR THE PREVENTATIVE TREATMENT OF PARKINSON'S DISEASE

(57)

The invention relates to the use of substituted 2-aminotetralines of general formula (I) as a medicament for the preventative treatment of Parkinson's disease.



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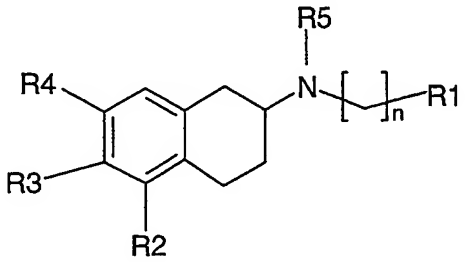

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(57) Abrégé/Abstract:
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ABSTRACT

The invention relates to the use of substituted 2-aminotetralines of general formula (I) as a medicament for the preventative treatment of Parkinson's disease.

Use of Substituted 2-Aminotetralines for the Preventative Treatment of Parkinson's Disease

Parkinson's disease occurs as a result of a chronic, progressive degeneration of neurones, the cause of which has not yet been completely clarified. It is clinically manifested in the form of the cardinal symptoms of resting tremors, rigidity, bradykinesia and postural instability.

Primarily used as medicaments for alleviating the motor symptoms are levodopa, dopamine agonists such as, for example, rotigotine, pramipexole, bromocriptine, ropinirole, cabergoline, pergolide, apomorphine and lisuride, anticholinergic agents, NMDA antagonists, β-blockers as well as the MAO-B inhibitor selegeline and the COMT inhibitor entacapone. Most of these active substances intervene in the dopaminergic and/or cholinergic signal cascade and symptomatically influence in this manner the motor disturbances that are typical of Parkinson's disease.

The therapy of Morbus Parkinson has, to date, been initiated with the onset of the cardinal symptoms. Morbus Parkinson is generally deemed to be clinically confirmed if at least two of the four cardinal symptoms (bradykinesia, resting tremors, rigidity and postural instability) can be determined and L-Dopa has an effect (Hughes, J Neurol Neurosurg Psychiatry 55, 1992, 181). Unfortunately, however, patients with Parkinson's disease only develop the motor disturbances once approximately 70 to 80% of the dopaminergic neurones in the substantia nigra (SN) have been irreversibly damaged (Becker *et al*, J Neurol 249, 2002, Suppl 3: III, 40; Hornykiewicz, Encyclopaedia of Life Science 2001, 1). The chances of a therapy with lasting effects are minimal at this time. It is thus desirable to commence therapy as early as possible.

Current clinical observations as well as anatomical and genetic research now show that it is possible to both diagnose patients with Parkinson's disease at an early stage and to identify high-risk patients.

The following, for example, can thereby be used as diagnostic markers:

- Biochemical markers, such as neuromelanin (Gerlach, Neurotox Res 5, 2003, 35; WO 02/31499), S-100 beta (Muramatsu, Glia 42, 2003, 307), alpha synuclein (WO 03/069332; WO 00/02053) or parkin protein (Sharma, Neurol Clin N Am 20, 2002, 759) and semaphorin (WO 03/007803).

- Genetic markers, such as the park genes 1-8 (Guttman, CMAJ 4, 2003, 168); CYP2D6-B (WO 03/012137), chromosome 2q 36-37 (Pankratz, Am J Hum Gen 72, 2003, e-pub), a-synuclein (Polymeropoulos, Science. 276, 1997, 2045) or mutations in CYP2D6-B and GSTM1 deletion (WO 03/012137).
- Imaging methods, such as ultrasound examination of the SN size, possibly in combination with other methods (Becker *et al*, J Neurol 249, 2002, Suppl 3: III, 40) or MRI (Hutchinson M, Raff U., J Neurol Neurosurg Psychiatry. 1999 Dec; 67(6): 815-8).
- Imaging methods such as PET or SPECT (Prunier C, Bezard E *et al*, Neuroimage. 2003 July; 19(3): 810-6).
- Sensory disorders or behavioural abnormalities, such as sleep and olfactory disorders, in particular, sleep disorders of the type "REM behaviour disorder", (Henderson, J Neurol Neurosurg Psychiatry 74, 2003, 956) or cognitive abnormalities (Rammsayer, Int J Neurosci. 91, 1997, 45).
- Organic problems such as constipation (Krygowska-Wajs, Funct Neurol 15, 2000, 41).
- Depression (Camicioli R. Drugs Today (Barc). 2002 Oct; 38(10): 677-86).
- Short-term movement anomalies, such as chorea or orthostatic abnormalities.
- Combinations of the aforementioned markers (Stern, Annals of Neurol 56, 2004, 169).

This thus creates the opportunity to influence the process of the disease at a point when more neurones are still present than is the case at the time of onset of several cardinal motor symptoms of Morbus Parkinson, and to thus protect a quantitatively greater number of neurones. It can be expected that the administration of an effective neuroprotective agent at an early stage will significantly delay the disease process: The earlier a therapy can be initiated, the greater the chances of a long-lasting prevention of the onset of symptoms that lower the quality of life.

There is thus a need for medicaments that are not only able to influence dopaminergic transmission and alleviate the symptoms of Morbus Parkinson in advanced stages, but that are also able to reverse, prevent or at least significantly slow down the progressive destruction of dopaminergic neurones in the early, largely motor-asymptomatic stages of Parkinson's disease (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

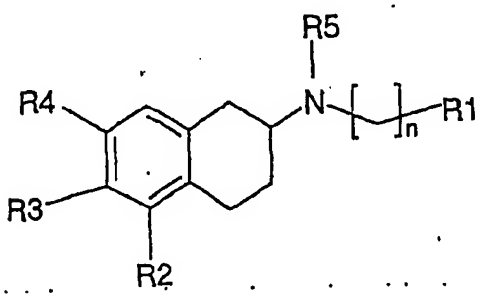
Substituted 2-aminotetralines are known from US 4,564,628, US 4,885,308, US 4,722,933 and WO 01/38321. These are substances having a dopaminergic effect, which are known for the symptomatic treatment of Parkinson's disease. In clinical studies, rotigotine [(-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol] in particular has proven itself to be an effective transdermally available anti-Parkinson drug. WO 02/

089777 describes, for example, the transdermal administration of rotigotine to patients with Parkinson's disease and the associated improvement in the UPDRS (Unified Parkinson's Disease Rating Scale) score. The UPDRS score is an important instrument for diagnosing and monitoring the progression and/or therapy of patients with Parkinson's disease (Fahn S, Elton RL, Members of the UPDRS Development Committee (1987) Unified Parkinson's Disease Rating Scale. In: Fahn, S, CD Marsden, DB Calne, M Goldstein (eds) Recent Developments in Parkinson's Disease. Vol. II. Macmillan Healthcare Information, Florham Park (NJ), pages 153-163, 293-304). However, the UPDRS score only records the effect of an active substance on the symptoms of Parkinson's disease. It does not allow any statements to be made with regard to whether or not an active substance has an influence on the destruction of dopaminergic cells, which is the underlying cause of the symptoms.

Metman *et al* (Clin Neuropharmacol 24, 2001, 163) also describe the effect of rotigotine on motor disturbances associated with Parkinson's disease. The treated patients already had pronounced dyskinesias, which were improved by administering rotigotine.

Thus, substituted 2-aminotetralines, in particular rotigotine, are known from the prior art as a dopamine agonist for the symptomatic treatment of Parkinson's disease. However, Parkinson medicaments that only have an effect on the symptoms do not promise any advantage with regard to the preventive treatment of Parkinson's disease since they do not have any influence on the destruction of dopaminergic cells or on the progression and/or onset of the disease.

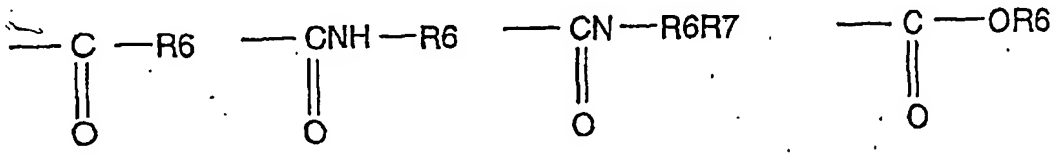
Experimental tests have now surprisingly shown that the substituted 2-aminotetralines of the general formula I



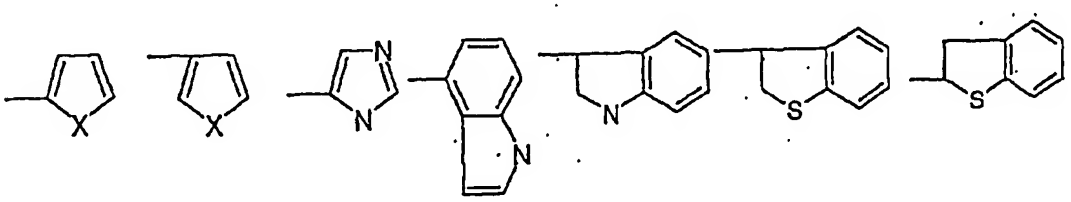
wherein

n is 1 to 5;

R2 is OA; R3 and R4 are each independently selected from H and OA; with A being selected from H, alkyl, alkoxymethyl or a group



wherein R6 and R7 are each independently alkyl, in particular C1-20 alkyl and particularly preferred C1-6 alkyl, or aryl, in particular optionally substituted phenyl;
R5 is a C1-3 alkyl;
R1 is a group selected from hydrogen, 3-pyridyl, 4-pyridyl, optionally substituted phenyl,



wherein X is selected from S, O or NH;

wherein the compound of formula I can be present as a racemate or as a pure (R)- or (S)-enantiomer,

as well as physiologically acceptable salts of these compounds,

which had hitherto only been used for the symptomatic therapy of Parkinson's disease, have neuroprotective properties and they can thus be used as a medicament and/or prophylactic agent for the prevention of dopaminergic cell loss in particular in very early stages of Parkinson's disease or in high-risk patients.

Figures

Fig. 1 shows representative examples of the neuroprotective effect of rotigotine measured on the basis of the density of the dopamine transporters as an indication of the density of the remaining nerve endings in the striatum.

Groups 1 to 7 were treated as follows: Group 1: untreated control group; Group 2: control group treated with a vehicle solution for rotigotine and MPTP; Group 3: MPTP treatment; Group 4: MPTP treatment plus rotigotine 0.3 mg/kg; Group 5: MPTP treatment plus

rotigotine 1.0 mg/kg; Group 6: MPTP treatment plus rotigotine 3.0 mg/kg; Group 7: treatment solely with rotigotine (3.0 mg/kg).

Fig. 2 shows dopamine transporter (DAT) binding in the dorsal and ventral part of the striatum in different groups by quantifying the DAT density according to an experiment as shown in Fig. 1. Bar graphs 1 to 7 correspond to groups 1 to 7 as shown in Fig. 1. The groups marked with * displayed a significant decline in DAT binding as compared to the control group 2. The groups marked with # displayed a significant gain in DAT binding as compared to the MPTP-treated Group 3.

Description of the Invention

Apoptotic processes are supposed to play an important role in the destruction of dopaminergic neurones in the pathogenesis of Parkinson's disease (Barzilai, Cell Mol Neurobiol 21, 2001, 215). Neuroprotective substances that can stop or even reverse dopaminergic cell destruction are thus desired. The MPTP model is thereby deemed to be predictive of the required neuroprotective characteristics (Dawson, Nature Neuroscience Supplement 5, 2002, 1058).

Rotigotine surprisingly shows the desired pharmacological profile in both an acute and a sub-acute MPTP model. The test results suggest that apoptotic processes are prevented by rotigotine.

The 2-aminotetralines according to the invention, in particular rotigotine, thereby display a neuroprotective effect in a mouse model of Parkinson's disease: Following the acute administration of MPTP, which causes Parkinson's syndrome in both humans and monkeys, the number of the degenerating neurones in the acute phase was measured on the one hand (Table 1) and the functional integrity of the striatum in the sub-acute phase was ascertained on the other by determining the density of the dopamine transporter in the terminal nerve endings (Figs. 1 and 2). It could be demonstrated in both cases that rotigotine had a neuroprotective effect: On the one hand, the number of degenerating neurones in the mesencephalon was reduced following the administration of rotigotine and on the other hand, the dopaminergic innervation of the striatum was almost completely maintained or restored.

Table 1: Number of degenerating neurones in the mouse, shown by FluoroJade staining

Group	No. of degenerating neurones	Standard deviation
1: Vehicle-treated control group	2.0	2.4
2: MPTP intoxication	73.5	34.0
3: MPTP intoxication + rotigotine 0.3 mg/kg	66.7	30.5
4: MPTP intoxication + rotigotine 1.0 mg/kg	76.8	41.6
5: MPTP intoxication + rotigotine 3.0 mg/kg	34.9	31.9
5: MPTP –vehicle + rotigotine 3.0 mg/kg	3.8	4.3

In a pilot study, the neuroprotective effect of rotigotine on monkeys was also examined.

In the model used, which reflects the progressive course of Morbus Parkinson in primates, monkeys (macaques) were injected with subliminal toxic doses of MPTP for several days. Parkinson's symptoms developed in the model over a period of approximately 2 weeks. As soon as a certain level of damage had been reached, rotigotine was injected daily in a formulation that produced a continuous plasma level over 24 hours. The MPTP injections were stopped as soon as the motor activity had been reduced to a certain extent (approximately 5 days later). The behaviour of the animals was assessed on a daily basis. Six weeks after the start of MPTP administration, the rotigotine injections were stopped and the animals were observed for a further two weeks without treatment. It was observed that the motor activity of the animals clearly improved during treatment and also in the following clearance phase.

A group of animals was killed at the end of both the rotigotine administration and the clearance phase, and the condition of the basal ganglia was histologically and biochemically examined. The density of the nerve endings in the striatum had significantly increased as compared to the untreated animals. The content of pre-pro-enkephalin, which is an indicator of the intact network in the "indirect pathway" of the basal ganglia, showed a tendency towards normalisation following treatment and the clearance phase.

The results show that the neuroprotective potential of rotigotine can also be proven in a primate model of Morbus Parkinson. A neuroprotective effect can therefore also be expected in humans.

Thus, with rotigotine and structurally related substituted 2-aminotetralines of the general formula I, active substances were provided for therapy, which are ideally suitable for

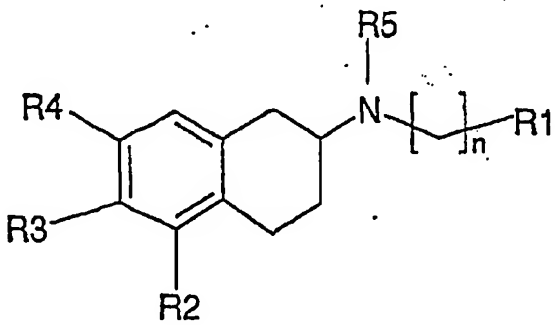
producing medicaments and/or prophylactic agents for the prevention of dopaminergic neurone loss.

A subject matter of the present application is therefore the use of substituted 2-aminotetralines of the general formula I, which is given below, as well as, in particular, rotigotine for the production of a medicament for the treatment or prevention of dopaminergic neurone loss in patients suffering from a neurodegenerative disease that is associated with increased dopaminergic cell destruction or in patients having an increased risk of augmented dopaminergic cell destruction.

Increased dopaminergic neurone loss regularly occurs in patients with Parkinson's disease, however, it is also frequently observed in other neurodegenerative diseases, for example, in alpha-synucleopathies or in Huntington's disease as well as in REM sleep disturbances and olfactory disorders.

As compared to the hitherto use of the aminotetralines of formula I, in particular rotigotine, which was limited solely to the symptomatic treatment of Parkinson's patients with motor disturbances, the prophylactic treatment of individuals displaying less than two of the cardinal symptoms of Parkinson's disease and who thus require neuroprotective, prophylactic therapy rather than symptomatic therapy, has been developed as a new area of use. As already described above, such individuals profit in particular from the neuroprotective effect of rotigotine since owing to the administration of rotigotine, dopaminergic cell loss is stopped or slowed down at a time when a higher number of dopaminergic neurones are still present than is the case in patients already displaying motor symptoms.

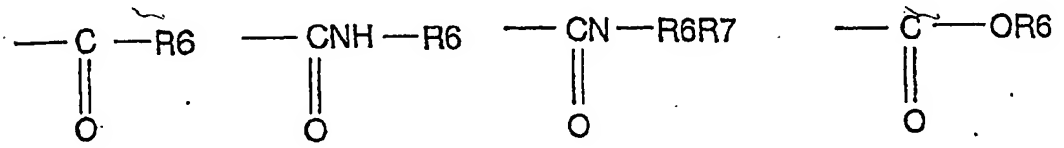
A subject matter of the invention is therefore the use of substituted 2-aminotetralines of the general formula I



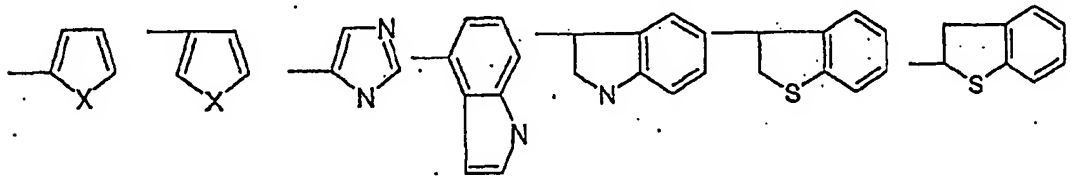
wherein

n is 1 to 5;

R2 is OA; R3 and R4 are each independently selected from H and OA; with A being selected from H, alkyl, alkoxymethyl or a group



wherein R6 and R7 are each independently alkyl, in particular C1-20 alkyl and particularly preferred C1-6 alkyl, or aryl, in particular optionally substituted phenyl;
R5 is a C1-3 alkyl;
R1 is a group selected from hydrogen, 3-pyridyl, 4-pyridyl, optionally substituted phenyl,

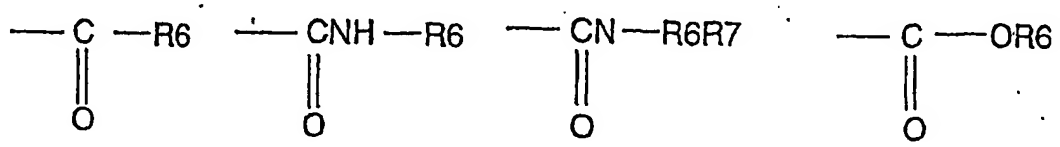


wherein X is selected from S, O or NH;

wherein the compound of formula I can be present as a racemate or as a pure (R)- or (S)-enantiomer,

as well as physiologically acceptable salts of these compounds, for the preventative treatment of Parkinson's disease, in particular for the prevention of dopaminergic cell loss in individuals in whom, before commencement of the preventive treatment, at least three of the four cardinal symptoms of the group bradykinesia, rigidity, resting tremors and postural instability are not yet present or are only rudimentary or partially present.

Compounds that are particularly suitable for the production of a neuroprotective agent or a prophylactic agent for Parkinson's disease are those in which R2 is an OA group and R3 and R4 are independently H or an OA group, it being particularly preferred for A to be a hydrogen atom or a group



in which R6 is a C1-20 alkyl, in particular C1-12 alkyl or C1-6 alkyl, phenyl or methoxyphenyl.

In another preferred embodiment of the invention R4 is H.
In another preferred embodiment of the invention R3 is H.
In another preferred embodiment of the invention R3 and R4 are both H.
In another preferred embodiment of the invention n = 1, 2 or 3, in particular n = 2 or 3.

R1 is preferably selected from the group H

und

wherein X is selected from S, O and NH and wherein it is especially preferred for X to be a sulphur atom.

It is especially preferred for R1 to be 2-thienyl.

In a further preferred embodiment of the invention, R5 is a C3-alkyl, in particular n-propyl.

In a further preferred embodiment of the invention, R1 is a 2-thienyl, R3 and R4 are both H, R5 is a C3 alkyl and n = 2.

In a particularly preferred embodiment of the invention, the racemate of (+/-) 5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, and especially preferred the pure S-enantiomer of this compound (rotigotine), is used for the production of the prophylactic agent for Parkinson's disease.

The terms "C1-20 alkyl", "C1-12 alkyl" and "C1-3 alkyl" are each to be understood as branched or non-branched alkyl groups with the corresponding number of C-atoms. For example, a "C1-20 alkyl" includes all alkyls with 1 to 20 C-atoms. The alkyls can be optionally substituted, e.g. with halogen. The alkyls are preferably present in non-substituted form.

The term "alkoxymethyl" is to be understood as the group –CH2-O-alkyl. A preferred alkyl is a C1-12 alkyl, a C1-6 alkyl or a C1-3 alkyl.